UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

September 10, 2019

MEMORANDUM

SUBJECT: Review of HeiQ's Response to Conditional Data Requirements for HeiQ AGS-20 and HeiQ AGS-20 U

PC Code: 072599	DP Barcode: D446021
Decision No.: 538714	Registration No(s).: 85249-1, 85249-2
Risk Assessment Type: Single Chemical	Case No.: NA
TXR No.: NA	CAS No.: NA
MRID No(s).: 50534301, 50534302	40 CFR: NA

FROM: Judy Facey, Ph.D., Toxicologist JUDY FACEY Digitally signed by JUDY FACEY Date 2019 09 11 12 18 45 -0400
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THROUGH: Andrew Shelby, Eco Team Risk Assessment Process Leader
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BACKGROUND

In response to a November 22, 2017 letter (U.S. EPA, 2017) and the Decision Document (U.S. EPA, 2011), the registrant HeiQ Materials AG submitted protocols and studies to address the Tier II data requirements. These data requirements are required to support the conditional registration of HeiQ AGS-20 (EPA Reg. No. 85249-1) and HeiQ AGS-20 U (EPA Reg. No. 85249-2). The registrant previously submitted studies to fulfill the Tier I data requirements, and one of the studies, the textile leaching study (MRID 49141001), indicated that silver particles were released from surface-coated textiles; as a result, Tier II testing was rendered necessary and must be conducted on the AGS-20 particles as well as the nanosilver inside.

The submissions for Tier II testing include two volumes of responses: Volume 1 and Volume 2. Volume 1 (MRID 50534301) consists of: 1) requests for extensions for protocols to address health effects and ecological/environmental effects; 2) MRID references for several characterization studies; and 3) an incomplete, draft protocol for an oral reproduction/developmental toxicity study in rats. Volume 2 (MRID 50534302) was submitted to fill potential gaps in the characterization requirement.

DETERMINATION

The Agency reviewed the draft protocol for oral rat reproduction/developmental toxicity study (Volume 1, MRID 50534301) and determined it to be unacceptable. In the Preface section of the protocol, the registrant recognized that the submitted draft protocol is not complete and requested additional time to complete the protocol.

To address the characterization requirement, Volume 1 lists the following studies (these are further discussed in the attached memo):

- MRID 48854401 – Particle Size and Diameter
- MRID 48957801 – Surface Area Determination
- MRID 48878801 – UV-Vis
- MRID 47544803[1] – Solubility-Release of Silver into Aqueous Media
- Supplement to MRID 47544803[1,2] – Additional measurements at pH 5 and 9

Volume 2 (MRID 50534302) provides further characterization data, including particle size and distribution, length and shape, crystallinity, surface area, and dissolution kinetics; it also estimates surface charge, zeta potential, and surface chemistry based on literature data for fumed silicas of similar structure and surface area. The Agency found two major issues with this study: 1) some of the tests were conducted on "product particles" formed after dispersion, and no explanation for the dispersion process was provided, and 2) literature values for surface charge, zeta potential, and surface chemistry for pure silica were assumed to be the same for HeiQ AGS-20. Rationale for bridging surface charge, zeta potential and surface chemistry or a new data study are needed, especially for a novel and poorly-understood active ingredient that comprises a large portion (20%) of the product, including the surface, and may result in significantly different surface properties. As a result, the Agency determined the Volume 2 study (MRID 50534302) to be unacceptable.

This memorandum is attached to a review of the characterization study (Volume 2, MRID 50534302).

[1] Incorrectly listed as MRID 48788003 in the submission
[2] This supplemental study has been assigned as MRID 48788003.

HeiQ AGS-20
EPA Registration Number: 85249-1

STUDY:	Response to EPA Conditional Data Requirements: Vol 2 Product Characteristics in Support of HeiQ AGS-20
DATA REQUIREMENT(S):	Non-guideline study
AUTHOR:	Dr. M. Height
STUDY NUMBER:	PT-019-18
STUDY COMPLETED:	May 24, 2010[3]
REVIEWED BY:	Sophia Hu, Chemist Risk Assessment & Science Support Branch Antimicrobials Division (AD) U.S. Environmental Protection Agency (USEPA)
PEER REVIEWED BY:	Andrew Byro, Ph.D., Chemist [redacted] Danielle McShan, Ph.D., Chemist Risk Assessment & Science Support Branch Antimicrobials Division (7510P) U.S. Environmental Protection Agency (USEPA)
DRAFT REVIEW COMPLETED:	6 September 2019

[3] Submitted as a "new" study with Volume 1 on February 22, 2018

EXECUTIVE SUMMARY

HeiQ Materials AG provided the Agency a physical-chemical characterization study (MRID 50534302) on HeiQ AGS-20 (EPA Reg. No. 85249-1), a silver-silica antimicrobial powder. Characterization tests for particle size and distribution, length and shape, crystallinity, surface area, surface charge, zeta potential, surface chemistry, and dissolution kinetics were provided for the silver product. The study is found to be unacceptable because 1) no explanation was provided for the "dispersion steps" used to break down the as-produced powder into the HeiQ AGS-20 product particles, and 2) surface charge, zeta potential, and surface chemistry were inferred from the literature when the product has not been determined to be sufficiently similar to allow for data bridging.

Two forms of HeiQ AGS-20—the HeiQ AGS-20 "product" particles and the "as-produced powder"—were analyzed in the study. The as-produced powder was analyzed in scanning electron microscopy (SEM) and laser scattering, while the HeiQ AGS-20 product particles was used in all other characterization tests. According to the study, the as-produced powder is the form prior to any dispersion step, and the HeiQ AGS-20 product particles is the resultant form after dispersion. However, no explanation was provided to describe this "dispersion," and the Agency requests a detailed procedure. The dispersion steps may alter the properties of the HeiQ AGS-20 product particles, and detailed information about these steps is needed. The Agency also requests clarification on whether the post-dispersion product particles were particles released (*i.e.*, leached) from treated textiles or represented particles that would become embedded in the textiles.

The results from the characterization study are summarized in Table 1. Microscopy shows silver particles distributed on the surface of a porous, amorphous silica matrix; the HeiQ AGS-20 product particles are in the form of aggregates ranging from 0.7 to 3.8 µm, while the silver particles inside are 5-20 nm. The as-produced powder was present as large agglomerates ranging from 10 to 50 µm in SEM. Laser scattering presents a similar size range, and the mean particle size is 20 µm. The HeiQ AGS-20 particles are approximately 1 µm wide and roughly spherical in the form of aggregates, and the amorphous silica matrix exhibits a fractal structure, similar to that of fumed silica. X-ray diffraction (XRD) confirms the presence of elemental silver particles in the powder. The specific surface area was calculated to be 181 ± 8 m^2/g. The dissolution kinetics of silver were submitted in an earlier study (MRID 48788003), which was accepted, and show a maximum dissolution of 5% after 168 hours.

Literature values for fumed silicas of similar structure and surface area were used to estimate surface charge, zeta potential, and surface chemistry of HeiQ AGS-20. The surface charge (at pH 7) was -1.5 to -3 $\mu C/cm^2$, and the zeta potential (at pH 7) was -35 to -40 mV. The surface chemistry was predicted to be dominated by hydroxyl groups with a concentration of 0.05-0.1 mg OH/m^2. However, use of the literature to determine the surface charge, zeta potential, and surface chemistry of HeiQ AGS-20 is unacceptable. The product is composed of 20% silver, some of which is distributed on the surface of silica, and therefore may not necessarily share similar properties as pure fumed silica; as a result, the literature values for fumed silicas may not hold true for HeiQ AGS-20.

As submitted, the study on HeiQ AGS-20 is unacceptable because 1) it does not provide any information about the dispersion of the "as-produced" powder, and 2) literature values were used to determine surface charge, zeta potential, and surface chemistry when such data bridging may not be appropriate. HeiQ AGS-20 contains 20% silver, including some on the surface of the silica matrix, which may alter the surface characteristics significantly enough to preempt data bridging to pure silica forms, and therefore, the surface charge, zeta potential, and surface chemistry will need to be determined experimentally.

CHARACTERIZATION OF HEIQ AGS-20

Applicant	HeiQ Materials AG
EPA Reg. No.	85249-1 (and -2)
Product Name	HeiQ AGS-20 (and HeiQ AGS-20 U)
DP Barcode	446021
MRID No.	50534302
PC Code	072599
CAS No.	NA

Table 1. Summary of Main Findings from Each Test.

Characteristic	Method	Findings
Electron Microscopy	TEM[1] & STEM[2]	HeiQ AGS-20 product particles show silver metal particles distributed within and on the surface of a porous, amorphous silicon dioxide matrix.
	SEM	As-produced powder shows large (10 to 50 µm) agglomerates of HeiQ AGS-20 particles
X-Ray Diffraction	Powder XRD	Silver metal particles (crystalline) inside amorphous silicon dioxide matrix
Size Distribution	TEM	0.7-3.8 µm (HeiQ AGS-20 product particle)
	TEM & STEM	5-20 nm (silver inside HeiQ AGS-20)
	SEM	10 to 50 µm (as-produced powder)
	Laser scattering	d_{50} = 20 µm (as-produced powder)
Length & Shape	TEM	Porous aggregate. Fractal solid with approximately spherical shape of ca. 1 µm diameter.
Specific Surface Area	Nitrogen BET	181 ± 8 m^2/g
Surface Charge	Literature (SiO_2)	-1.5 to -3 $\mu C/cm^2$ (at pH 7)
Zeta Potential	Literature (SiO_2)	-35 to -40 mV (at pH 7)
Surface Chemistry	Literature (SiO_2)	Dominated by hydroxyl (OH) groups (0.05 to 0.1 mg OH/m^2)
Silver Dissolution Kinetics	Quantitative	Max. 5% after 168 hours (67 mg/L from 1,300 mg/L total available Ag)

[1]Transmission Electron Microscopy
[2]Scanning Transmission Electron Microscopy

Lack of Information Regarding Dispersion Steps for "Product Particles" Versus "As-Produced" Powder

HeiQ AGS-20 product particles were analyzed in all the characterization tests, except scanning electron microscopy (SEM) and static light scattering (SLS), in which the as-produced powder was examined. The study states that the "[a]s-produced powder is the form of material obtained directly from the production process and is the form of the product powder handled by workers prior to any dispersion step (*e.g.*, compounding into polymers or dispersion in liquids)" (MRID 50534302, p. 7). HeiQ AGS-20 product particles, on the other hand, are the form "after dispersion steps that break down the as-produced agglomerated powder into the discrete unit particles" (p. 7). No explanation was provided for these dispersion steps, and a detailed procedure is requested on exactly how the as-produced powder was dispersed.

Based on the 2016 product label, it is assumed that the "as-produced powder" is the form placed into water-soluble packets and the "HeiQ AGS-20 product particles" are the resultant form when the packets dissolve into water for coating/finishing purposes or melt with polymers for fiber spinning processes. Thus, depending on whether the HeiQ AGS-20 product particles are used for coating/finishing treatment of textiles or for fiber spinning processes, there are two possible types of dispersion the product can undergo. The Agency requests a detailed explanation for the dispersion steps used, and the following information should be included:

- Type of dispersion (coating/finishing or fiber spinning) and justification for why that type was selected (*i.e.*, was assumed to be representative of both types in real-world scenarios)
- Medium used to disperse the as-produced powder
- Amount of the medium
- Amount/concentration of polyethylene oxide (substance used as a water-soluble packet)
- Types of polymers/other substances present in the medium (if any) and their respective amounts/concentrations
- Length of time the particles stayed in the medium, starting with the release of the particles from the packet and ending with the termination of the manufacturing process (when final treated textiles were produced)
- Means of dispersion (shaking, sonication, *etc.*)
- Temperature
- pH
- Any other relevant conditions or information

The steps used to disperse the as-produced powder in the study should reflect the actual conditions in the workplace (*i.e.*, in mixing vessels and hoppers). Significant differences in the dispersion process may result in different properties of the HeiQ AGS-20 product particles. No definite conclusions can be made about the HeiQ AGS-20 product because of the lack of information on the dispersion of the as-produced powder.

Particle Size and Distribution

Size measurements were obtained for the HeiQ AGS-20 product particles, the silver particles only, and the as-produced powder. The as-produced powder comes straight from the production process and is the form handled by workers prior to any dispersion step. The HeiQ AGS-20 product particles are the final form after dispersion steps take place, which break down the agglomerates into discrete aggregates. TEM (Transmission Electron Microscopy) and STEM (Scanning Transmission Electron Microscopy) were conducted on the HeiQ AGS-20 product particles and the silver particles inside, while SEM and laser scattering were conducted on the as-produced powder.

Using low and high magnifications, TEM micrographs demonstrate silver metal particles distributed on the surface of silica aggregates. Particle size of the HeiQ AGS-20 particles (as aggregates) ranges from 0.7 to 3.8 µm. STEM micrographs show a clear contrast between the metallic silver particles and the amorphous silica matrix. The size distribution of the silver particles inside the HeiQ AGS-20 particles is 5-20 nm. In SEM, the as-produced powder was shown to be agglomerates of HeiQ AGS-20 particles, ranging from 10 to 50 µm. The electron microscopy results from the study are given in Table 2.

Table 2. Electron Microscopy Particle Size Distribution Report Form on HeiQ AGS-20.

<table>
<tr><th>Item</th><th colspan="2">Description</th><th>Comment</th></tr>
<tr><th colspan="4">Identity of Test Material</th></tr>
<tr><td>Composition</td><td colspan="2">20% silver
[redacted]</td><td>Powder</td></tr>
<tr><td>Source</td><td colspan="2">HeiQ AGS-20</td><td>TEM and STEM on HeiQ AGS-20 product particles. SEM on as-produced powder.</td></tr>
<tr><td>Lot/Batch ID</td><td colspan="2">Not provided.</td><td></td></tr>
<tr><th colspan="4">Sample Preparation</th></tr>
<tr><td>Sample Amount</td><td colspan="2">Not provided.</td><td></td></tr>
<tr><td>Dispersion Medium</td><td colspan="2">Not provided.</td><td></td></tr>
<tr><td>Means of Dispersion</td><td colspan="2">Not provided.</td><td></td></tr>
<tr><th colspan="4">Analytic Method</th></tr>
<tr><th></th><th>TEM</th><th>STEM</th><th>SEM</th></tr>
<tr><td>Measurement Principles</td><td colspan="2">Operating power at 300kV</td><td>Not provided.</td></tr>
<tr><td>Instrument/Model</td><td colspan="2">FEI Tecnai F30 FEG microscope</td><td>Not provided.</td></tr>
<tr><td>Calculation Method</td><td>Size distribution on HeiQ AGS-20 product particles and silver particles inside</td><td>Size distribution on silver particles inside HeiQ AGS-20 product particles</td><td>Size distribution on as-produced powder</td></tr>
<tr><td>Limits of Measurement</td><td colspan="2">0.14 nm to >50 µm</td><td></td></tr>
<tr><td>Calibration or Standardization</td><td colspan="3">Not provided.</td></tr>
<tr><th colspan="4">Results</th></tr>
<tr><td>Distribution Basis</td><td colspan="3">Number</td></tr>
</table>

Mean Diameter (µm)	Not provided.		
Standard Deviation (µm)	Not provided.		
Min/Max of Size Range (µm)	**TEM**	**STEM**	**SEM**
HeiQ AGS-20	0.7-3.8 µm	--	--
Silver metal	5-20 nm	5-20 nm	--
As-produced powder	--	--	10-50 µm
Quality Assurance			
Reference Materials	NIST-NCL PCC-7. "Measuring the Size of Nanoparticles Using Transmission Electron Microscopy (TEM)."		
Additional Information/Comments			
TEM beam current settings, objective lens excitation, and diffraction aperture size (if used) should also be reported (NIST).			

Static light scattering (SLS) was also used to measure the as-produced powder, and the results are provided in Table 3. One measurement was taken after each 20-second interval, from 0 (no ultrasonication) to 100 seconds. The size distributions at each interval were unimodal, suggesting low polydispersity. The particle size decreased as the time duration of ultrasonication increased, but this decrease became smaller after every increment of 20 seconds ultrasonication. The difference in particle size between 80 and 100 seconds (<1 µm) was smaller than that between 20 and 40 seconds (~3 µm); 100 seconds appeared to be sufficient time for ultrasonication. After 100 seconds of ultrasonication, the mean particle size was 20 µm, with the majority of particles falling within 10-50 µm, which is consistent with the SEM measurements.

Validation of the sample concentration is normally recommended to determine the optimal concentration. However, the Agency determined this is not necessary because SEM measurements were provided, and the SLS sizes are consistent with them.

Table 3. Static Light Scattering Particle Size Distribution Report Form on HeiQ AGS-20.

Item	Description	Comment
Identity of Test Material		
Composition	20% silver [redacted]	Powder
Source	HeiQ AGS-20	As-produced powder
Lot/Batch ID	HQ-RCC-080311	
Sample Preparation		
Sample Amount	Not provided	
Dispersion Medium	Ultrapure water	
Means of Dispersion	Ultrasonication up to 100 seconds at 22°C	
Analytic Method		
Measurement Principles	D10, D16, D50, D84, D90, D99 static light scattering with aqueous dispersion	Measurements taken after 0, 20, 40, 60, 80, and 100 seconds of ultrasonication
Instrument/Model	Sympatec HELOS (light diffraction)	

Item		Description		Comment		
Identity of Test Material						
Calculation Method		Average particle size in microns, intensity-based				
Limits of Measurement		0.10-100 µm				
Calibration or Standardization		Not provided.				
Precision: Repeatability or Reproducibility		Not provided.				
Results						
Ultrasonication Duration (sec)	**0**	**20**	**40**	**60**	**80**	**100**
Min/Max of Size Range (µm)	<0.45-87.5	<0.45-73.5	<0.45-73.5	<0.45-61.5	<0.45-61.5	<0.45-51.5
10% diameter (µm)	11.4	10.5	9.9	9.5	9.2	9.0
50% diameter (µm)	30.0	26.0	23.7	22.1	21.0	20.2
90% diameter (µm)	54.3	47.1	41.9	38.8	36.0	35.0
99% diameter (µm)	73.6	61.4	57.6	52.4	49.2	47.6
Quality Assurance						
Reference Materials		NIST-NCL PCC-7. "Measuring the Size of Nanoparticles Using Transmission Electron Microscopy (TEM)."				
Additional Information/Comments						
pH of the solution should be provided.						

The measurements in this particle size study are consistent with those in a previously submitted study (MRID 48854401) that was conducted on the as-produced powder. According to MRID 48854401, the D10-D90 size range was roughly 10-100 µm, with an average of 37 ± 17 µm (volume-based). SEM sizes ranged from 0.5-135 µm (mostly between 0.5 and 50 µm), with an average of 3.1 ± 0.7 µm, and TEM sizes of the nanosilver itself ranged from 0.6-72 nm, with an average of 4 nm[4]. Average XRD size was 35.6 ± 4.1 nm.

Length and Shape

Based on the SEM and TEM images, the HeiQ AGS-20 product particles are roughly spherical aggregates with a diameter of approximately 1 µm. The amorphous silica matrix also exhibits a fractal structure that is usually observed with fumed silica (Evonik Industries, p. 36-37, 40).

It is clear that dispersion broke down the as-produced agglomerated powder into discrete (~1-µm) unit particles. The dispersion did not appear to significantly change the size of the silver particles inside, since the TEM sizes of the silver particles in MRID 48854401 (0.6-72 nm, average of 4 nm, on the as-produced powder) were fairly consistent with the TEM/STEM measurements in this study MRID 50534302 (5-20 nm, on the post-dispersion product particles).

[4] According to the study (MRID 48854401), this is a conservative size distribution analysis, based on silver metal particles observed only in the high magnification TEM images. Larger particles (>100 nm) were present in low magnification images but were not considered in the size distribution. These larger particles account for the larger average sizes observed in XRD and oxygen chemisorption.

X-Ray Diffraction

Powder X-ray diffraction (XRD) was conducted on the HeiQ AGS-20 particles and confirms the presence of elemental silver metal in the powder. The XRD pattern shows three peaks at approximately $2\theta = 38°$, $48°$, and $68°$. These peaks agree with the literature peak values (Theivasanthi & Alagar, 2012) for elemental metallic silver and indicate a face-centered cubic crystal structure. No peaks appeared for silicon dioxide because it is amorphous.

Surface Area

The specific surface area (SSA) of the HeiQ AGS-20 product was reported to be 181 ± 8 m^2/g (Table 4). This is very close to the value in a previously submitted study (MRID 48957801), which indicates an average SSA of 184 ± 14 m^2/g. MRID 48957801 also calculated the average silver size to be 32 ± 3 nm, based on oxygen pulse chemisorption. The SSA values in both studies are similar to those (~200 m^2/g) of fumed silicas of similar amorphous silica structure and specific surface area.

Table 4. Surface Area Report Form on HeiQ AGS-20.

Item	Description	Comment
Identity of Test Material		
Composition	20% silver [redacted]	Powder
Source	HeiQ AGS-20	
Lot/Batch ID	HQ-ZHAW-033 – HQ-ZHAW-033-47	
Sample Preparation		
Sample Amount	~0.04-0.05 g	
Means of Dispersion	Not provided.	
Treatment Conditions	Dried at 150°C for 16 hours under N_2	
Analytic Method		
Measurement Principles	Brunauer-Emmett-Teller (BET) surface area analysis	Analysis adsorptive: N_2
Instrument/Model	Quantachrome Instruments, NovaWin2	
Software Version	NovaWin2 Version 9.0	
Calculation Method	Volume of analysis gas adsorbed versus relative pressure	
Limits of Measurement	0.01 m^2/g to no known upper limit	
Calibration or Standardization	Not provided.	
Precision: Repeatability or Reproducibility	15 replicate measurements	
Results		
Surface Area	181 ± 8 m^2/g	

Item	Description	Comment
Quality Assurance		
Reference Materials	ASTM B922.1272. "Standard Test Method for Metal Powder Specific Surface Area by Physical Adsorption."	

Surface Charge, Zeta Potential, and Surface Chemistry

Surface charge and zeta potential were not measured directly from the HeiQ AGS-20 product but deduced from literature values for fumed silicas of very similar structure (porous and amorphous) and specific surface area (~200 m^2/g). Based on peer-reviewed studies (Gun'ko, 2005) on various fumed silicas and the experimental surface area of HeiQ AGS-20, the registrant estimated the surface charge of HeiQ AGS-20 to be -1.5 to -3 $\mu C/cm^2$ and the zeta potential to be -35 to -40 mV (both values at pH 7). As for surface chemistry, fumed silica has a surface density of approximately 2-3 OH groups per square nm (Mueller *et al*., 2003), also equivalent to 0.05-0.1 mg/m^2 demonstrated by fumed silica with specific surface areas of 100-300 m^2/g (Gun'ko, 2005). Thus, HeiQ AGS-20 was estimated to have a surface hydroxyl concentration of 0.05-0.1 mg/m^2.

However, the extrapolation of literature values for fumed silicas to determine the surface charge, zeta potential, and surface chemistry of the HeiQ AGS-20 particles is not adequate. The estimations are based on the assumption that HeiQ AGS-20 is dominated by the silica structure, sharing similar surface properties as fumed silica. Nevertheless, many silver particles are present on the surface of the silica matrix, as indicated in the TEM and STEM micrographs; even the study author noted the silver particles were "distributed on the surface of the silicon dioxide" (p. 5 of study). Accounting for a relatively large percentage composition (20%) of the product, including the surface, the silver could have a significantly large influence on the surface properties. As a result, the literature data on pure fumed silicas may not hold true for nanosilica-silver composites. Furthermore, silver has a positive charge and could cause the zeta potential to become less negative or positive even. One study (Zielecka, 2011) demonstrates that a silver content of 6.93% in silica flipped the zeta potential from negative to positive as well as increased the absolute value of the zeta potential, resulting in increased stability of the colloid. Although that study used a different synthesis method (sol-gel process), which may or may not be a factor in the silver's effect on zeta potential, it still leaves the possibility that the silver in HeiQ AGS-20 may cause a similar phenomenon. Not only can the silver content influence the surface properties, but the dispersion steps used in the characterization (and real-world applications) of HeiQ AGS-20 may as well. For instance, a study (Górnicka, 2016) found the average size of Aerosil 200—a fumed silica product that is similar in structure and specific surface area to HeiQ AGS-20—in water was 592 nm at 0 hours but decreased to 191 nm after 48 hours; the absolute value of the zeta potential also decreased after 48 hours from 12.6 mV to 9.1 mV. The zeta potential of -12.6 mV is significantly smaller (*i.e.*, less stable) than the estimated range of -35 to -40 mV that was predicted in this study. Instead of bridging the literature data for pure fumed silicas to HeiQ AGS-20, the registrant should conduct actual tests to find the surface charge, zeta potential, and surface chemistry. For the zeta potential test, the zeta potential should be measured against a wide range of pH and time, too.

Dissolution Kinetics

The dissolution kinetics of silver were measured in a previously submitted study (MRID 48788003), which was reviewed and accepted (U.S. EPA, 2012). The study results are summarized in Table 5 and Figure 1, and they indicate a maximum dissolution of 5% after 168 hours (7 days) with the highest ion release occurring in aqueous sulfate buffer solutions (moderately hard water system). Another dissolution kinetics study (MRID 49327301) found a maximum silver dissolution of 36% in distilled water and 10% in moderately hard reconstituted water after 21 days.[5] These percentages are much higher than in this current study (using MRID 48788003) and could be due to differences in sample concentrations, measurement/analytical methods, ionic strength, as well as the inherent issues/unreliability mentioned in MRID 49327301.

The dissolution kinetics study (MRID 48788003) appears to be conducted on the post-dispersion powder,[6] which may exhibit different dissolution kinetics behavior from that of leached particles (or even secondary nanoparticles formed from the release of ionic silver). The registrant previously submitted another dissolution kinetics study (MRID 49327301[5,7]) on silver particles released from HeiQ AGS-20 and a textile leaching study (MRID 49141001) on silver particles released from treated textiles. Although both studies had issues (U.S. EPA, 2016), the Agency decided not to require a new dissolution kinetics study on the released silver from textiles, as it is not expected to add to what the previous studies already provided.

Table 5. Dissolution Kinetics Report Form on HeiQ AGS-20 (taken from MRID 48788003).

Item	Description	Comment
Identity of Test Material		
Composition	20% silver [redacted]	Powder
Source	HeiQ AGS-20	
Lot/Batch ID	HQ-RCC-080311	
Sample Preparation		
Sample Amount	~2 g	Nominal concentration of silver in final solution: 1,300 mg Ag/L
Dispersion Medium	Phosphate buffer solutions at pH 4 and 8 at 37°C. Sulfate buffer solutions at pH 6 and 9 at 20°C.	Phosphate buffer was used to simulate physiological conditions, and sulfate buffer (of moderate

[5] Note: The study was problematic such that its reliability was reduced (U.S. EPA, 2016)

[6] Post-dispersion product particles, instead of as-produced powder, were assumed to be used because the study author is M. Height. This author also wrote the surface area study (MRID 48957801), which was most likely conducted on the product particles because of very similar SSA values between that study and this current study (MRID 50534302). If the as-produced powder was used in the surface area study, the SSA value would be expected to be much larger.

[7] Two other dissolution kinetics studies were provided (MRIDs 49203401 and 49165501), but they were found to have essentially identical information as MRID 49327301, so only MRID 49327301 is discussed in this report. It is the latest and corrected version of MRID 49203401 and provides a slightly more complete summary than MRID 49165501.

Item	Description	Comment
	Deionized water at pH 5.8 at 20°C.	hardness) was used to simulate environmental conditions.
Means of Dispersion	Test item was mixed with 300 mL of the matrix, then shaken at 150 rpm	Shaking water bath for phosphate buffer and flatbed shaker for sulfate buffer.
Duration of Dispersion Treatment	Shaken up to 7 days, protected from light	
Analytic Method		
Measurement Principles	Inductively coupled plasma mass spectroscopy (ICP-MS)	
Instrument/Model	Perkin Elmer Sciex Elan 6100	
Software Version	Version 2.3.2	
Calculation Method	Silver concentration was measured after 0, 3, 6, 12, 18, 24, 72, and 168 hours. Release rate (relative to initial silver concentration) was calculated.	Prior to analysis, 10 mL of sample was filtered through 0.45 µm nitrocellulose filter and digested with 5% nitric acid.
Limits of Measurement	Lowest limit of detection = 0.012 mg Ag/L. Lowest limit of quantification = 0.04 mg Ag/L.	Based on calibration
Calibration or Standardization	Silver ICP standard of 1.003 mg/L	
Precision: Repeatability or Reproducibility	3 replicates at each time interval	

Results (% of total silver added to the solution)

Time (h)	Phosphate buffer pH 4, 37°C	Phosphate buffer pH 8, 37°C	Sulfate buffer pH 6, 20°C	Sulfate buffer pH 9, 20°C	Water pH 5.8, 20°C
0	2.18	0.23	3.46	3.49	2.97
3	1.83	0.19	3.98	3.96	3.14
6	1.35	0.18	4.09	4.11	3.17
12	0.93	0.18	4.14	4.19	3.25
18	0.64	0.18	4.34	4.39	3.41
24	--[8]	--[8]	4.29	4.31	3.36
72	0.66	0.19	4.73	4.76	3.78
168	0.62	0.2	4.94	5.03	3.95

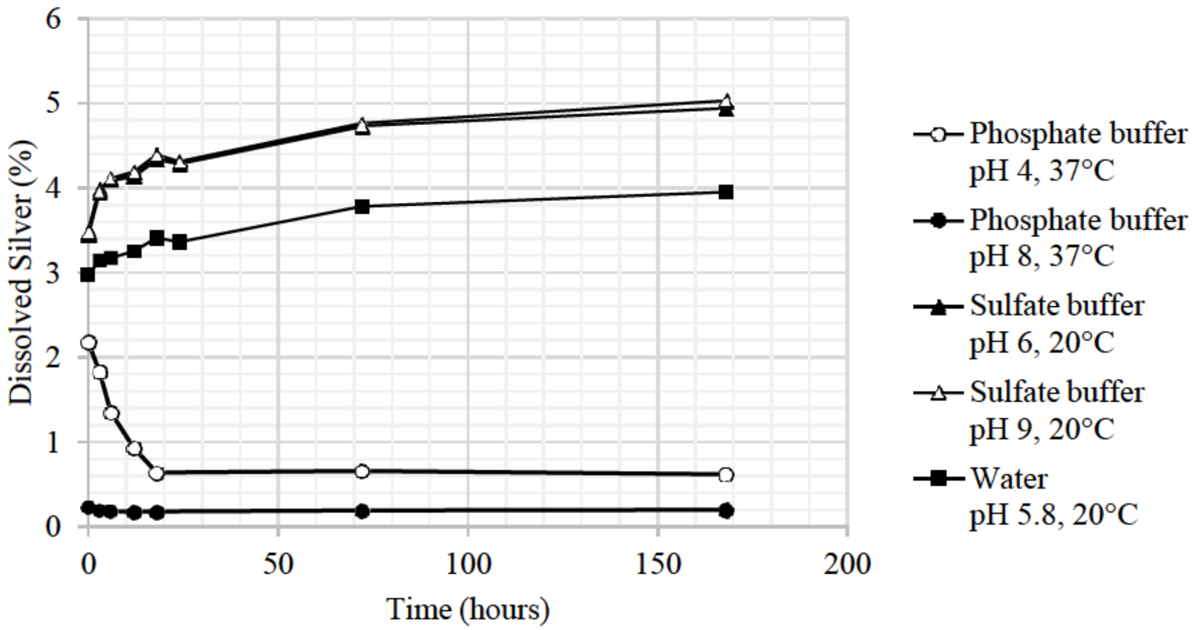
Quality Assurance

Reference Materials	ASTM B922.1272. "Standard Test Method for

[8] Reported as outlier, not used.

Item	Description	Comment
	Metal Powder Specific Surface Area by Physical Adsorption.”	

Figure 1. Dissolution kinetics of silver from HeiQ AGS-20 into various solutions expressed as percent of total silver added to the solution.



CONCLUSIONS

Risk Assessment and Science Support Branch of Antimicrobials Division finds the study (50534302) on HeiQ AGS-20 to be <u>unacceptable</u> because of two major deficiencies: 1) no explanation was provided for the dispersion steps used to break down the as-produced powder, and 2) surface charge, zeta potential, and surface chemistry were not determined experimentally. Results from TEM, STEM, SEM, and SLS show the HeiQ AGS-20 product particles to be roughly spherical aggregates of approximately 1 µm wide, the silver inside ranging from 5-20 nm, and the as-produced powder to be agglomerates of 1-50 µm size. XRD confirms the presence of elemental (metallic) silver particles inside an amorphous silica matrix. The specific surface area was calculated to be 181 ± 8 m^2/g. From a previously submitted study (MRID 48788003, accepted), the silver had a maximum dissolution of 5% after 168 hours, with the highest ion release occurring in moderately hard water. Literature values for fumed silicas of similar structure and specific surface area were used to estimate the surface charge, zeta potential, and surface chemistry of HeiQ AGS-20, but such predictions are not justifiable. Comprising 20% of the product composition and being present on the surface of HeiQ AGS-20, the silver may have a significant influence on the surface properties to make data bridging to pure silica inappropriate; unless the registrant provides a strong justification for such data bridging, it will need to determine the surface charge, zeta potential, and surface chemistry experimentally.

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